

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-302**

**ADMINISTRATIVE DOCUMENTS**

**Office of Post-Marketing Drug  
Risk Assessment  
(OPDRA)**

# Memo

**TO:** Jonathan Wilkin, M.D.  
Director, Division of Dermatologic and Dental Drug Products  
HFD-540

**FROM:** David Diwa, Pharm.D.  
Safety Evaluator, Office of Post-Marketing Drug Risk Assessment  
HFD-400

**THROUGH:** Jerry Phillips, R.Ph.  
Associate Director, Office of Post-Marketing Drug Risk Assessment  
HFD-400

**CC:** Millie Wright,  
Project Manger  
HFD-540

**DATE:** October 11, 2001

**RE:** OPDRA Consult 00- 0223, Elidel (Pimecrolimus Cream 1%) NDA 21- 302

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This memorandum is in response to a request from your Division on September 25, 2001, for a re-review of the proprietary name, Elidel. The expected action date on this application is on or before December 15, 2001.

OPDRA has identified an additional proprietary name Foradil, which has a potential for confusion with Elidel since our initial review. Foradil (formoterol fumarate) is a  $\beta_2$ -agonist inhalation powder packaged with an inhaler device. The product is indicated for the maintenance treatment of asthma and prevention of exercise induced bronchospasm. Elidel and Foradil are formulated in different dosage forms. Moreover, the methods of administration and indication for the two products are different. Based on information currently available, we believe that Foradil does not pose significant

risk of confusion with Elidel. Therefore, we have no objections to the use of the proprietary name Elidel.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3231.

**APPEARS THIS WAY  
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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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David Diwa  
10/12/01 09:05:47 AM  
PHARMACIST

Jerry Phillips  
10/12/01 10:08:12 AM  
DIRECTOR

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**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED:** 08/14/00

**DUE DATE:** 03/09/01

**OPDRA CONSULT #:** 00-0223

**TO:**

Jonathan Wilkin, M.D.  
Director, Division of Dermatologic & Dental Drug Products  
HFD-540

**THROUGH:**

Millie Wright  
Project Manager  
HFD-540

**PRODUCT NAME:** Elidel (pimecrolimus cream) 1%  
**NDA:** 21-302

**MANUFACTURER BY:** Novartis Pharma GmbH, Wehr/Baden, Germany  
**DISTRIBUTED BY:** Novartis Pharmaceutical Corp., East Hanover, NJ

**SAFETY EVALUATOR:** David Diwa Pharm.D.

**SUMMARY:** In response to a consult from the Division of Dermatologic & Dental Drug Products (HFD-540), OPDRA has performed a review of the proposed proprietary name Elidel to determine the potential for confusion with marketed drug products and pending drug names.

**OPDRA RECOMMENDATION:**

OPDRA has no objection to use of the proprietary name, Elidel.

- FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW**  
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.
- FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW**  
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.
- FOR PRIORITY 6 MONTH REVIEWS**  
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

\_\_\_\_\_  
Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3242  
Fax: (301) 480-8173

\_\_\_\_\_  
Martin Himmel, MD  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B03  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** 01/17/01  
**NDA:** 21-302  
**NAME OF DRUG:** Elidel (pimecrolimus cream) 1%  
**NDA, HOLDER:** Novartis Pharmaceutical Corporation

**I. INTRODUCTION:**

This consult is written in response to an August 14, 2000 request from the Division of Dermatologic and Dental Drug Products (HFD-540) for an assessment of the proposed proprietary name, Elidel. The sponsor submitted the name for review in phase III of IND — and filed the NDA on December 15, 2000.

**PRODUCT INFORMATION**

Elidel (pimecrolimus cream) 1% is a macrolactam derivative and selective inhibitor of pro-inflammatory cytokines. It is also a mediator of T cell and mast cell activity. The product is proposed for use in the short-term and long-term management of atopic dermatitis (eczema) in pediatric — and adult patients. Each gram of Elidel will contain 10 mg of the active ingredient pimecrolimus in a whitish cream base. The recommended dose is a twice-daily application to the affected areas. The sponsor has proposed packaging the product in tubes of 15 g, 30 g and 100 g.

**II. RISK ASSESSMENT:**

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts<sup>1,2,3</sup> as well as several FDA databases<sup>4</sup> for existing drug names which sound alike or look alike to Elidel to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>5</sup>. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient)

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<sup>1</sup> MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

<sup>2</sup> American Drug Index, 42<sup>nd</sup> Edition, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>4</sup> The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the proposed name Elidel.

**A. EXPERT PANEL DISCUSSION**

The expert panel consists of members of OPDRA’s medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

Several names identified by Expert Panel were thought to have the potential for confusion with Elidel. These products are summarized in the table below.

DDMAC has no objection to the proposed drug name Elidel.

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Elidel	Pimecrolimus cream 1%	Apply to affected area BID for atopic dermatitis	
Elocon	Mometosone furoate 0.1% cream/lotion	Apply to affected area 2-3 times daily	*LA
Gliadel	Carmustine (BiCNU) 7.7 mg wafer	Single treatment dose with 8 wafers	*LA
Elimite	Permethrin 5% cream	Apply as directed to affected area	*LA
Elavil	Amitriptyline, 10, 25, 50, 75, 100 & 150mg tablets; 10 mL injectable 10 mg/mL.	30-100 mg/day single/divided doses	*SA/LA
Parlodel	Bromocriptine ; 2.5 mg cap, 5 mg tab	1.25 mg BID	*LA
Plendil	Felodipine, 2.5, 5, 10 mg extended release tabs	2.5-10 mg tabs	*LA
Isordil	Isorsobide dinitrate, sustained release 40 mg cap; 5, 10, 20, 30 & 40 mg tabs	5-40 mg tid or qid	*LA

\*SA = Sound-alike  
\*LA = Look-alike

**B. PRESCRIPTION ANALYSIS STUDIES**

**1. Methodology:**

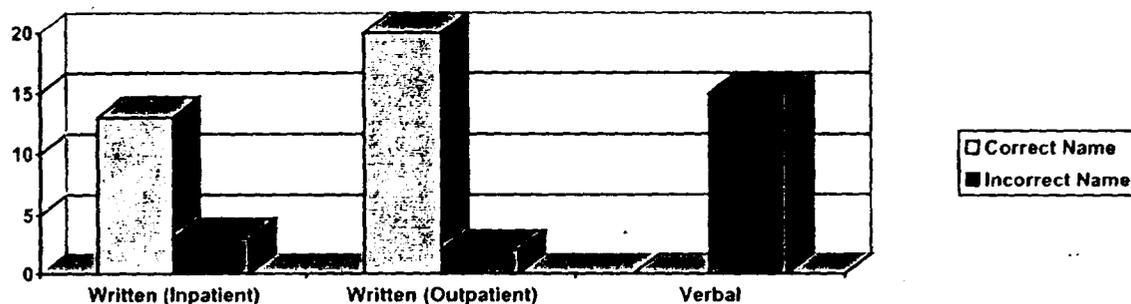
Three studies were conducted by OPDRA involving 90 health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of name confusion between Elidel and other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Elidel (see page 4). These prescriptions were scanned into a computer and subsequently delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Elidel use BID	Outpatient Verbal RX: Elidel use BID
Inpatient RX: Discharge meds: Elidel use BID	

2. The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	29	16 (55%)	13 (81%)	3 (19%)
Written Outpatient	30	22 (73%)	20 (91%)	2 (9%)
Verbal	31	15 (48%)	0 (0%)	15 (100%)
Total	90	53 (59%)	33 (62%)	20 (38%)



Thirty eight percent of all study participants responded incorrectly to the name Elidel. Written and verbal scores of the incorrect responses are summarized in Table II on page 5.

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Table II

Incorrectly Interpreted	
<u>Written Outpatient</u>	Eidel
	Eudel
<u>Verbal Outpatient</u>	Aladel (2)
	Aldelal
	Alodal
	Alodel
	Alodol (2)
	Allodar
	Alledel
	Allodel (2)
	Allerdill
	Allordil
	Eladel
	Iladel
<u>Written Inpatient</u>	Elidil (2)
	Elidelare

All incorrect responses were misspelled or phonetic variations of the proposed drug name. Results of the verbal prescription study showed that in a majority of incorrect responses, the first letter of the proposed name Elidel was substituted with the letter A. The inaccurate interpretations of the proposed drug name did not overlap with an existing approved drug product. We recognize that high scores of incorrect interpretations would be common for all unapproved products because healthcare professionals are not familiar with the name.

**C. SAFETY EVALUATOR RISK ASSESSMENT**

The OPDRA expert panel identified Elocon, Gliadel, Elimate, Elavil, Parlodel, Plendil and Isordil as marketed products with sound-alike/look-alike qualities to Elidel. While Elidel is applied topically, four of the identified products, Gliadel, Parlodel, Plendil and Isordil are administered orally. Moreover, the four products have different strengths, dosing schedule and belong to a different pharmacological class when compared with Elidel. Gliadel (carmustine) is an antineoplastic agent administered in 7.7 mg single treatment dose wafers. Parlodel (bromocriptine) is an antiparkinson's agent available in tablet formulation. Plendil (felodipine) is an oral antihypertensive and Isordil (isorsobide dinitrate) is an oral vasodilator. The potential for name confusion between these four products and Elidel appears unlikely.

Elocon (mometosone furoate) is a corticosteriod topical cream/lotion. Both Elocon and Elidel are formulated as topical creams and can be used to treat atopic dermatitis. Elocon is available as a 0.1% topical cream and Elidel will be marketed as a 1% topical cream. Despite these similarities, there are no strong sound-alike qualities between Elidel and Elocon. Moreover, the products can be differentiated when scripted (Eidel 0.1% vs Elocon 1%). Additionally, the potential for serious outcome if confusion occurs with these two products is low.

Elimite (permethrin) is a scabicide/pediculicide 5% topical cream formulation. It has look-alike qualities to Elidel. However, the two products have different indications for use, strengths, directions for use and pharmacologic activity. The potential for name confusion between Elimite and Elidel appears low.

Elavil (amitriptyline) has strong sound-alike/look-alike qualities to Elidel. Elavil is a tricyclic antidepressant available in both tablet and injectable dosage forms. The two drug products are used in the long-term management of disease conditions. Elavil is available in 100 mg tablet formulation and Elidel is available in 100 g cream tubes. A family physician, nurse practitioner or a physician assistant can prescribe both Elavil and Elidel. In chronic disease states where patients may become familiar with directions for use, it is not uncommon for prescribers to write, "use as directed". However, the potential for a mix-up between these two products appears to be low due to differences in use and route of administration.

#### D. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Elidel, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels, carton and insert labeling and identified several areas of possible improvement, which might minimize potential user error.

##### 1. CONTAINER/CARTON LABELING

- a. Revise to read: Usual Dosage: Apply twice daily to affected area. See package insert.
- b. Revise to read: Each gram contains 10 mg pimecrolimus. In addition, each gram contains benzyl alcohol....

##### 2. PACKAGE INSERT (Dosage and Administration)

A wide range of healthcare practitioners including dermatologists, family practitioners, pediatricians, nurse practitioners and physician assistants will likely prescribe Elidel. There is a potential risk for the statement "Elidel may be used on all skin surfaces" to draw varying interpretations. To remind the reader of general exceptions to the use of Elidel (e.g. cutaneous viral infections), \_\_\_\_\_  
Therefore we suggest the following:

Elidel may be used on all \_\_\_\_\_ skin surfaces \_\_\_\_\_

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**III. RECOMMENDATIONS:**

1. OPDRA has no objection to the proposed proprietary drug name, Elidel.
2. OPDRA recommends implementation of labeling changes outlined in the review to improve the safe use of this product.

We would appreciate feedback of the final outcome of this consult. We would also be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact David Diwa at 301-827-0892.

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David Diwa, Pharm.D.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

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Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

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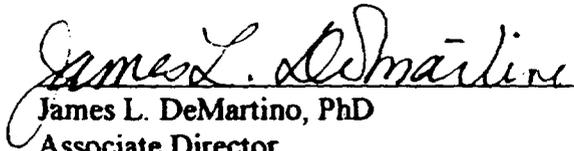
**Drug Regulatory Affairs**

**SDZ ASM 981 (pimecrolimus) Cream 1%**

**NDA 21-302**

**Debarment Certification**

NOVARTIS PHARMACEUTICALS CORPORATION hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

 Date December 6, 2000  
James L. DeMartino, PhD  
Associate Director  
Drug Regulatory Affairs

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EXCLUSIVITY SUMMARY for NDA # 21-302 SUPPL #

Trade Name Elidel Cream, 1% Generic Name pimecrolimus

Applicant Name Novartis Pharmaceuticals Corporation HFD-540

Approval Date December 13, 2001

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/X/ NO /\_\_\_/

b) Is it an effectiveness supplement? YES /\_\_\_/ NO /X/

If yes, what type(SE1, SE2, etc.)? N/A

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /X/ NO /\_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study. N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: N/A

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /X/ NO //

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /X/

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /X/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES // NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.) N/A

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s) N/A

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes." N/A-this is a new chemical entity

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans.. other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation. N/A-new chemical entity

YES // NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO //

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /X/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

N/A

YES /\_\_\_/ NO /\_\_\_/

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /X/

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #B305

Investigation #2, Study #B307

Investigation #3, Study #B316

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 B305 YES /\_\_\_/ NO /X/

Investigation #2 B307 YES /\_\_\_/ NO /X/

Investigation #3 B316 YES /\_\_\_/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:N/A

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 B305 YES /\_\_\_/ NO /X/

Investigation #2 B307 YES /\_\_\_/ NO /X/

Investigation #3 B316 YES /\_\_\_/ NO /X/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:N/A

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study #B305

Investigation #2, Study #B307

Investigation #3, Study #B316

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #        YES /X/ NO /\_\_\_/ Explain:

Investigation #2

IND #        YES /X/ NO /\_\_\_/ Explain:

Investigation #3

IND #        YES /X/ NO

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1

YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_

Investigation #2

YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or

sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/      NO /X/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer  
Title:

Date

Signature of Office or Division Director

Date

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/s/

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Jonathan Wilkin  
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## Printable Pediatric Page

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### PEDIATRIC PAGE

NDA Number: 021302 Trade Name: ELIDEL (PIMECROLIMUS) CREAM 1%  
 Supplement Number: 000 Generic Name: PIMECROLIMUS  
 Stamp date: 12/15/00 Action Date: 12/15/00  
 Supplement Type: N  
 COMIS Indication: ATOPIC DERMATITIS

**Indication #1: For short-term and intermittent long-term therapy in the treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 2 years of age and older**

**alternative,** - Date Entered: 11/25/01  
 in whom the use of

Status: Pediatric Ranges were specified.

Range #1 Status: Completed

[Edit this Range](#) [Delete this Range](#)

Range Values: Minimum: 2 yr Maximum: Adult

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Date

11/27/01

**Elidel™ (pimecrolimus) Cream 1%**

**NDA 21-302**

**Patent Information**

**Author(s):** Carol Loeschorn  
**Document type:** Registration  
**Document status:** Final  
**Release date:** October 30, 2000  
**Number of pages:** 2

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Confidential  
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without the consent of Novartis Pharma AG

**APPEARS THIS WAY  
ON ORIGINAL**

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Time Sensitive Patent Information  
pursuant to 21 C.F.R. 314.53  
for  
NDA # 21-302

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The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: Elidel™  
Active Ingredient(s): pimecrolimus  
Strength: 1%  
Dosage Form: Cream  
Approval Date: Pending

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- A. U.S. Patent Number: 5,912,238  
Expiration Date: June 15, 2016  
Type of Patent: Compound per se; Pharmaceutical composition/formulation;  
and method of use in treating atopic dermatitis  
Patent Owner: Novartis AG  
Lichtstrasse 35 CH-4002  
Basle, Switzerland
- B. The undersigned declares that the above U.S. Patent Number 5,912,238 covers the pharmaceutical composition, formulation and/or method of use of Elidel™ (pimecrolimus) Cream 1%. This product is the subject of this application for which approval is being sought.

Signed: Carl A. Lechner 12/1/2000

**Labeling Review**  
**Addendum to NDA 21-302**

**NDA #21-302**

**Review start: 11/7/01**

**Review Completed: 11/26/01**

*Reviewer's Comment: The following is the final draft label submitted by the sponsor on June 19, 2001. It is followed by the label that is being recommended for approval by the division. It thus includes all the changes that were recommended by this reviewer and the clinical team and these changes were decided at the labeling meetings of 11/16/01 and 11/20/01. These labels are followed by the patient package insert (PPI) and the recommendations for changes by this reviewer. Deletions to the (PPI) are denoted by ~~strikeout~~ and additions by shadowing.*

**Sponsor's Label**

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**APPEARS THIS WAY  
ON ORIGINAL**

WITHHOLD 27 PAGE (S)

Draft

Labeling

[ ]

Denise Cook, M.D.  
Medical Officer, Dermatology

cc: HFD-540  
HFD-340  
HFD-540/CSO/WrightM  
HFD-540/CHEM/Pappas  
HFD-520/MICRO/  
HFD-540/PHARM/HillB  
HFD-540/MO/CookD  
HFD-880/Biopharm/GhoshT  
HFD-725/Stats/FriedlinV  
In DFS 11/26/01

For Concurrence Only:  
HFD-540/Clinical TL/LukeM  
HFD-540/DivDir/WilkinJ

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ON ORIGINAL**

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Denise Cook  
11/26/01 02:44:24 PM  
MEDICAL OFFICER

This is the labeling addendum to the Elidel NDA

Markham Luke  
11/26/01 04:30:39 PM  
MEDICAL OFFICER  
Labeling Review including PPI. Concur with changes to labeling.

Jonathan Wilkin  
11/29/01 05:56:21 PM  
MEDICAL OFFICER  
Additional labeling changes are occurring as discussions with Sponsor  
proceed. This review captures the initial draft labeling  
sent to the Sponsor for comment.

**APPEARS THIS WAY  
ON ORIGINAL**

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 Novartis Pharmaceuticals Corp.  
 Elidel Cream 1%

14-SEP-2001

FDA CDER EES  
 ESTABLISHMENT EVALUATION REQUEST  
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Application: NDA 21302/000 Action Goal:  
 Stamp: 15-DEC-2000 District Goal: 16-AUG-2001  
 Regulatory Due: 15-OCT-2001 Brand Name: ELIDEL (PIMECROLIMUS) CREAM 1%  
 Applicant: NOVARTIS PHARMACEUTICALS CORP Estab. Name:  
 NO CITY, , XX Generic Name: PIMECROLIMUS  
 1S  
 Priority: 540 Dosage Form: (CREAM)  
 Org Code: Strength: 1%  
 Application Comment:  
 FDA Contacts: M. WRIGHT (HFD-540) 301-827-2020, Project Manager  
 E. PAPPAS (HFD-540) 301-827-2066, Review Chemist  
 W. DECAMP II (HFD-540) 301-827-2041, Team Leader

Overall Recommendation: ACCEPTABLE on 27-AUG-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [ ]

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_  
 Responsibilities: \_\_\_\_\_  
 Profile: CFN OAI Status: NONE  
 Estab. Comment: THE NDA LISTED CFN \_\_\_\_\_ FOR A FACILITY WITH NO STREET ADDRESS  
 IN THIS DATA BASE. (on 05-JAN-2001 by E. PAPPAS (HFD-540) 301-827-2066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
SUBMITTED TO DO	11-JAN-2001	GMP			EGASM
DO RECOMMENDATION	26-JAN-2001			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 1/29/99					
OC RECOMMENDATION	26-JAN-2001			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 9617734  
 NOVARTIS PHARMA GMBH  
 OEFLINGER STRASSE 44  
 WEHR, BADEN, GM D-79664

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_  
 Responsibilities: FINISHED DOSAGE MANUFACTURER  
 FINISHED DOSAGE PACKAGER  
 Profile: OIN OAI Status: NONE  
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
SUBMITTED TO DO	11-JAN-2001	PS			EGASM
ASSIGNED INSPECTION	16-JAN-2001	PS			EGASM
INSPECTION SCHEDULED	18-MAY-2001		05-JUL-2001		IRIVERA
INSPECTION PERFORMED	05-JUL-2001		05-JUL-2001		EGASM
DO RECOMMENDATION	23-AUG-2001			ACCEPTABLE INSPECTION ACCEPTABLE	GARCIA
OC RECOMMENDATION	24-AUG-2001			ACCEPTABLE DISTRICT RECOMMENDATION	GARCIA

Establishment: 9692043

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NOVARTIS PHARMA INC (CIBA)  
 SCHAFFHAUSERSTRASSE  
 CH-4332 STEIN, , SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE  
 FINISHED DOSAGE RELEASE TESTER

Profile: CRU OAI Status: NONE

Estab. Comment: THIS FACILITY IS RESPONSIBLE FOR OF THE DRUG SUBSTANCE AND  
 THE TESTING OF THE EXCIPIENTS FOR THE FINISHED PRODUCT. (on 05-  
 JAN-2001 by E. PAPPAS (HFD-540) 301-827-2066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
SUBMITTED TO DO	11-JAN-2001	GMP			EGASM
ASSIGNED INSPECTION	25-JAN-2001	GMP			EGASM
INSPECTION SCHEDULED	29-MAY-2001		29-JUN-2001		IRIVERA
INSPECTION PERFORMED	28-JUN-2001		28-JUN-2001		IRIVERA
NO FD-483 WAS ISSUED, FIRM IS ACCEPTABLE.					
DO RECOMMENDATION	02-AUG-2001			ACCEPTABLE	EGASM
OC RECOMMENDATION	02-AUG-2001			INSPECTION ACCEPTABLE	DAMBROGIOJ
DISTRICT RECOMMENDATION					

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
SUBMITTED TO DO	11-JAN-2001	GMP			EGASM
ASSIGNED INSPECTION	25-JAN-2001	GMP			EGASM
INSPECTION SCHEDULED	29-MAY-2001		29-JUN-2001		IRIVERA
INSPECTION PERFORMED	28-JUN-2001		28-JUN-2001		IRIVERA
NO FD-483 WAS ISSUED, FIRM IS ACCEPTABLE.					
DO RECOMMENDATION	02-AUG-2001			ACCEPTABLE	EGASM
OC RECOMMENDATION	02-AUG-2001			INSPECTION ACCEPTABLE	DAMBROGIOJ
DISTRICT RECOMMENDATION					

Establishment: 9611204

NOVARTIS PHARMA INC (SANDOZ)  
 LICHSTRASSE 35, ST. JOHANN SITE  
 BASEL, , SZ 4002

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 FINISHED DOSAGE RELEASE TESTER

Profile: CRU OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
SUBMITTED TO DO	11-JAN-2001	GMP			EGASM
ASSIGNED INSPECTION	25-JAN-2001	GMP			EGASM
INSPECTION SCHEDULED	29-MAY-2001		21-JUN-2001		IRIVERA
INSPECTION PERFORMED	28-JUN-2001		21-JUN-2001		IRIVERA
NO FD-483 WAS ISSUED, FIRM IS ACCEPTABLE.					
DO RECOMMENDATION	02-AUG-2001			ACCEPTABLE	EGASM
INSPECTION					

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OC RECOMMENDATION 02-AUG-2001 ACCEPTABLE DAMBROGIOJ  
 DISTRICT RECOMMENDATION  
 Profile: CTL OAI Status: NONE  
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
SUBMITTED TO DO	11-JAN-2001	GMP			EGASM
ASSIGNED INSPECTION	25-JAN-2001	GMP			EGASM
INSPECTION SCHEDULED	29-MAY-2001		21-JUN-2001		IRIVERA
INSPECTION PERFORMED	28-JUN-2001		21-JUN-2001		IRIVERA
NO FD-483 WAS ISSUED, FIRM IS ACCEPTABLE.					
DO RECOMMENDATION	02-AUG-2001			ACCEPTABLE	EGASM
OC RECOMMENDATION	02-AUG-2001			INSPECTION ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: 9612715

NOVARTIS PHARMA INC (SANDOZ)  
 RINGASKIDDY/CORK, RINGASKIDDY, EI

DMF No: AADA:  
 Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
 Profile: CTL OAI Status: NONE  
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
SUBMITTED TO DO	11-JAN-2001	GMP			EGASM
DO RECOMMENDATION	25-JAN-2001			ACCEPTABLE	EGASM
BASED ON FILE REVIEW					
BASED ON EI OF 5/19/00					
OC RECOMMENDATION	25-JAN-2001			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment: 9614433

NOVARTIS PHARMANALYTICA SA  
 LOCARNO, , SZ

DMF No: AADA:  
 Responsibilities: DRUG SUBSTANCE STABILITY TESTER  
 Profile: CTL OAI Status: NONE  
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
OC RECOMMENDATION	11-JAN-2001			ACCEPTABLE	EGASM
				BASED ON PROFILE	

Establishment:

[ ]

DMF No: AADA:  
 Responsibilities: \_\_\_\_\_  
 Profile: OIN OAI Status: NONE

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 Novartis Pharmaceuticals Corp.  
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Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
SUBMITTED TO DO	10-JAN-2001	GMP			FERGUSONS
DO RECOMMENDATION	07-FEB-2001			ACCEPTABLE BASED ON FILE REVIEW	DPAGANO
OC RECOMMENDATION	07-FEB-2001			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment:

[ ]

DMF No:

AADA:

Responsibilities:

\_\_\_\_\_

Profile: CTL

OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2001				PAPPAS
SUBMITTED TO DO	11-JAN-2001	GMP			EGASM
ASSIGNED INSPECTION	16-JAN-2001	GMP			EGASM
INSPECTION SCHEDULED	09-MAR-2001		16-MAR-2001		IRIVERA
INSPECTION PERFORMED	19-MAR-2001		16-MAR-2001		IRIVERA
RECOMMEND APPROVAL.					
DO RECOMMENDATION	17-APR-2001			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	18-APR-2001			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

APPEARS THIS WAY  
 ON ORIGINAL



*Wright*

Food and Drug Administration  
Rockville MD 20855

Michael T. Jarratt, M.D.  
DermResearch, Inc.  
Building 3, Suite 120  
8140 North Mopac  
Austin, Texas 78759-8858

JUL 26 2001

Dear Dr. Jarratt:

Between June 19 and 21, 2001, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol # CASM981.B307) of the investigational drug Elidel Cream 1%, performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Martinez discussed with you his inspectional observation that two subjects were randomized prior to completion and evaluation of baseline laboratory tests. We acknowledge your promise to make corrections/changes in your procedures to ensure that the finding noted above is not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Martinez during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me by letter at the address given below.

Sincerely yours.

*/S/*

Antoine El-Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, MD 20855



Harry Irving Katz, M.D.  
7205 University Avenue, NE  
Fridley, Minnesota 55432

Food and Drug Administration  
Rockville MD 20857

JUL 25 2001

Dear Dr. Katz:

Between June 11 and 14, 2001, Ms. Sharon L. Matson, representing the Food and Drug Administration (FDA), met with Dr. Steven E. Kempers and his staff to review your conduct of a clinical study (protocol # CASM981.B307) of the investigational drug Elidel Cream 1%, performed for Novartis Pharmaceuticals Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Matson presented and discussed with Dr. Steven E. Kempers and his staff her inspectional observations. The discussion included the following:

- a) Global Assessment ratings were incorrectly reported in the case report form (CRF) for subjects #7, #8, and #21.
- b) Not all adverse events were reported in the CRFs for subjects #1, #2, #5, #9 and # 20.
- c) Not all concomitant medications were reported for subjects #1#2, #5, #9 and # 20 and #24.

Please make corrections/changes in your procedures, to ensure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Matson during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me by letter at the address given below.

Sincerely yours,  
*/S/*

Antoine El-Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, MD 20855